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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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ALLEMAGNE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Stent with rough surface and its manufacture

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EP-Patent Application
JOMED GmbH
Our Ref.: G 2617 EP

Stent with rough surface and its manufacture

The present invention relates generally to stents which are implantable or deployable in a vascular or endoluminal location within the body of a patient to maintain the lumen open and unoccluded at that location, and in particular to improvements in stents.

First of all, stents are widely used for numerous applications where the stent is placed in the lumen of a patient and expanded. Said stents may be used in coronary or other vasculature as well as within the urinary tract, the bial tract and the intestinal tract among other body passageways and conduits.

Commonly, stents are cylindrical members which are expanded from reduced diameters to enlarged diameters. Frequently, such stents are placed on a balloon catheter with the stent in a reduced diameter state. To prevent that the balloon is damaged because of sharp corners and burrs on the surface of the stent and further to avoid thrombus formation, stents are highly polished. This is done for example by sandblasting the surface to remove said imperfections and polishing the stent afterwards to get a smooth surface. Unfortunately, the balloon catheder mounted stent can be dislodged from the uninflated balloon as a result of the navigation through the vessel of the body to the preselected site for deployment because of the highly polished surface. Furthermore, the polished and smooth surface used to avoid thrombus formation has the disadvantage, that endothelial cells have difficulties to ingrow the stent which can result in that restenosis occurs.

In the prior art, some stents are sandblasted on their interior surface to improve stent retention on the balloon.

In US–A-6 254 631 B1 a stent is disclosed, wherein the exterior surface of the stent is polished such that a smooth surface finish is achieved. The interior surface having a rough

surface finish is rougher than the surface finish of the exterior surface to enhance the friction between the stent and the balloon.

Further in US-A-6 217 607 B1 a stent is disclosed which is provided with a first layer of nobel metal. Further a second outermost layer is provided which is composed of a ceramic like metal such as iridium oxid or titanium nitrate. The second layer is formed with a rough surface to provide an increased friction factor and retention on a balloon during advancement of the stent delivery system through the vessel.

In WO 99/07308 a stent is disclosed wherein a portion of a stent supporting structure is encapsulated with a thin flexible coating made of a polymer which can be used as a carrier for supporting therapeutic agents and drugs. Furthermore, the supporting structure, preferably only the portion which is not encapsulated by the thin flexible coating, is further processed to form a porous exterior surface. Said porous exterior surface renders the exposed portions of the supporting structure, such as the proximal and distal ends more biocompatible by promoting tissue in-growth while reducing the formation of blood clots.

Said stents of the prior art have the disadvantage that they are complicated to manufacture and expensive.

The object of the present invention is therefore to provide an improved stent, which can be manufactured at low costs and which can further avoid thrombus formation and a stenosis.

This object is achieved by the features of the claims.

According to the invention a stent is provided comprising at least an outer surface portion which is roughened to a predetermined extent and wherein a drug or a therapeutic agent can be applied to said surface.

This has the advantage, that the stent does not have to be provided with an additional drug deposit e.g. a polymer layer suitable to carry a drug or therapeutic agent. Instead the drug can be applied directly to the rough surface and released over a predetermined time after the stent has been placed in a desired location of a lumen. Furthermore a roughened exterior

surface decrease in-stent restenosis, since cells can attach more easily to said surface than to a smooth one which results in that endothelial ingrowth is accelerated. Intima cells can grow on the rough surface and attach themselves, wherein the endothelialization of the vessel or lumen is promoted. The endothelial cell layer is very smooth and therefore thrombus formation and a stenosis can be avoided.

In a preferred embodiment the drug e.g. Tacrolimus is applied to the rough surface by spraying. This has the advantage, that the application of the drug is effective, simple and inexpensive.

In a further preferred embodiment of the invention imperfections such as e.g. burrs are removed before at least a portion of the surface of the stent is roughened. This has the advantage that the surface can be roughened more uniform which leads to better flow dynamics. Thus less turbulences can occur on the surface which results in a reduction of restenosis.

In a preferred embodiment of the invention the surface is roughened to a predetermined extent by sandblasting. Moreover, sandblasting results in an improvement of the fatigue behaviour. Further the durability of the stent and the surface bonding can be improved. The rough surface also provides an increased surface area for an attachment of a drug or therapeutic agent. Further a stent with a thinner wall with higher radial force and therefore less material can be achieved which also leads to a decrease of restenosis. With sandblasting the surface can be better controlled and produced and further a more uniform and trauma less surface can be achieved.

Furthermore, the use of corundum for sandblasting results in a surface which is technically different from a normal sandblasted surface. It has the advantage that less energy has to be used and/or less time for this finishing sandblasting than for a sandblasting process to remove burrs. Further the sandblasted surface has less depth with regard to the "cavities". Furthermore the chemical behaviour of such a stent is different from commonly known electropolished stents. The surface chemistry is different due to the incorporation of sand particles into the surface. An immediately repassivated surface leads to more chemically stable passive layers than surfaces which have been passivated in equilibrium.

When blasting the surface the resulting lattice imperfections (e.g. vacancy, dislocation) and further possible phase transitions lead to an increased surface energy and thus to a surface which is chemically more reactive. This can lead to a faster chemical running and/or to additional chemical reactions than in the equilibrium.

In a further preferred embodiment the stent is annealed after the surface has been roughened to a predetermined extent to make him more flexible.

The invention will now be described with reference to the figures, in which

figures 1 to 7 show sandblasted exterior and side surfaces of a stent in different resolutions,

figures 8 to 14 show sandblasted interior and side surfaces of a stent in different resolutions,

figure 15 shows a table 1, including a list of samples of stents which are used for studying content and release of a drug applied on their surface,

figure 16 show tables 2 and 3 wherein the results of several samples regarding their content are listed,

figure 17 show tables 4 and 5, wherein samples are studied regarding release of the drug Tacrolimus, and

figure 18 shows a diagram, wherein the release of Tacrolimus of samples with respect to time is shown.

In an embodiment of a stent according to the invention, as shown in figures 1 to 14, the complete surface, i.e. exterior surface, interior surface and side surfaces, is sandblasted by using corundum. It is obvious that the invention is not limited to said embodiment and that also only portions of the surface can be roughened.

In figures 15 to 18 content and release of samples of stents are studied. In this connection normal manufactured stents are compared with stents which are further processed according

to the invention. Based on the examples shown in the figures the improved properties of stents according to the invention can be demonstrated.

EP-Patent-Application
JOMED GmbH
Our Ref.: G 2617 EP

Claims :

1. A stent for placement in a body lumen which is expandable from a contracted state to an expanded state, the stent comprising :

a) an exterior surface, an interior surface and side surfaces,

b) wherein at least a portion of the exterior surface is roughened to a predetermined extent for coating with a drug.

2. A stent according to claim 1, comprising at least a portion of the interior surface which is roughened to a predetermined extent.

3. A stent according to claims 1 or 2, comprising at least a portion of the side surfaces which is roughened to a predetermined extent.

4. A stent according to any of claims 1 to 3, wherein the outer surface and/or the inner surface and/or side surfaces are coated with a drug, preferably Tacrolimus.

5. A stent according to any of claims 1 to 4, wherein said stent comprises a stainless steel.

6. A balloon catheder device for inserting a tubular stent, comprising a stent as defined in any of claims 1 to 5.

7. A method for fabricating a stent for placement in a body lumen, said method comprising the following steps:

a) forming a tube which can be employed from a contracted state to an expanded state, said stent having an exterior surface, an interior surface and side surfaces,

b) roughening of at least a portion of the exterior surface to a predetermined extent,

c) coating of said surface with a drug.

8. A method according to claim 7, wherein at least a portion of the interior surface is roughened to a predetermined extent.

9. A method according to claims 7 or 8, wherein at least a portion of the side surfaces is roughened to a predetermined extent.

10. A method according to any of claims 7 to 9, wherein the surface is roughened to a predetermined extent by sandblasting.

11. A method according to any of claims 7 to 10, including an additional step d) after step a) wherein imperfections such as sharp edges and burrs are removed from the surface of the tube.

12. A method according to claim 11, wherein the imperfections are removed by burring.

13. A method according to claim 11 or 12, wherein the imperfections are removed by electropolishing.

14. A method according to any of claims 7 to 13, wherein the imperfections are removed by sandblasting.

15. A method according to any of claims 10 to 14, wherein sand is used for sandblasting.

16. A method according to any of claims 10 to 15, wherein glass beads are used for sandblasting.

17. A method according to any of claims 10 to 16, wherein corundum is used for sandblasting.

18. A method according to any of claims 7 to 17, wherein the drug is Tacrolimus.

19. A method according to any of claims 7 to 18, wherein the drug is applied by spraying on the roughened surface.

20. A method according to any of claims 7 to 19, wherein the tube is annealed.

Stent with rough surface and its manufacture

A stent is provided wherein at least an outer surface portion is roughened to a predetermined extent and wherein a drug or a therapeutic agent can be applied to said surface. This results in an improved stent, which can be manufactured at low costs and which can further avoid thrombus formation and a stenosis.

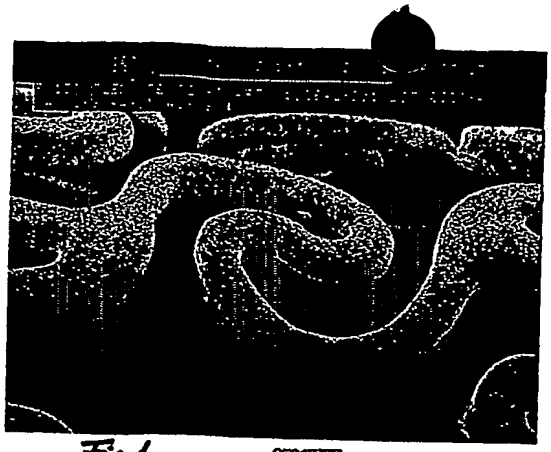


Fig 1 05017.TIF 688×560×256 gr

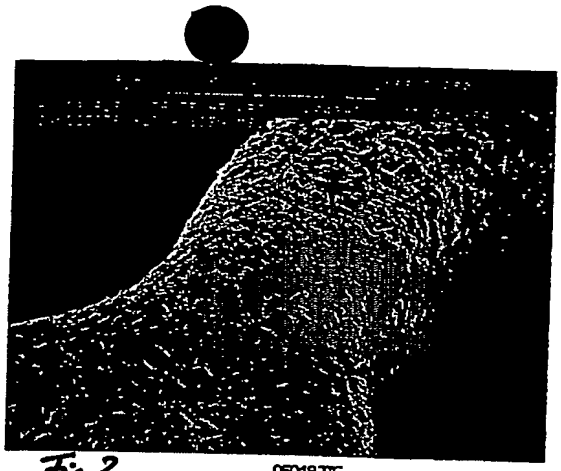


Fig 2 05018.TIF 688×560×256 gr

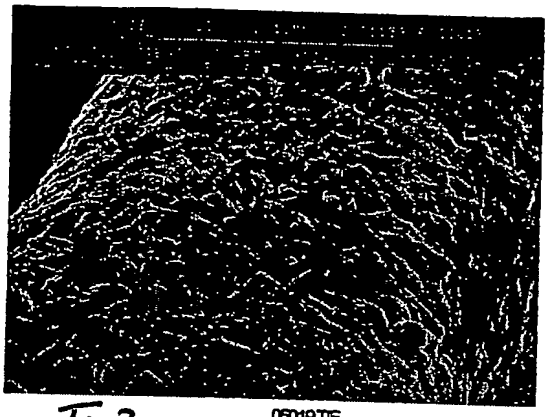


Fig 3 05019.TIF 688×560×256 gr

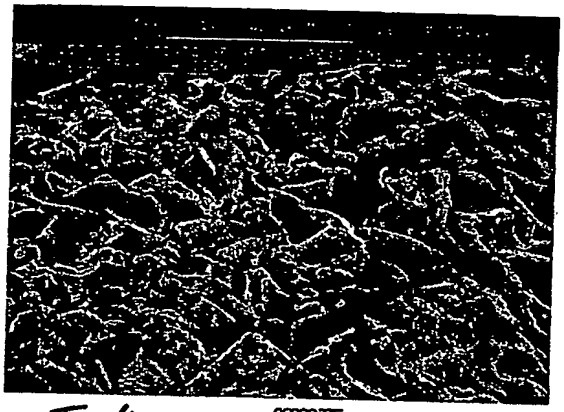
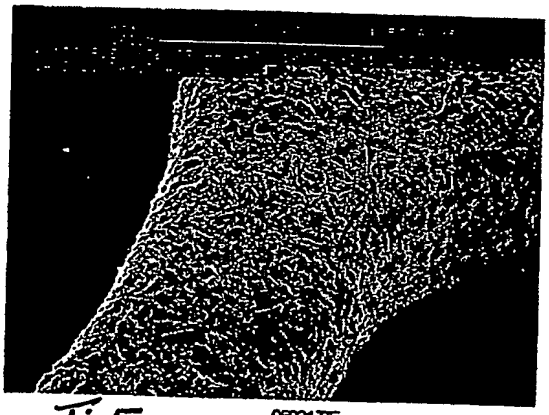


Fig 4 05020.TIF 712×572×256 gr



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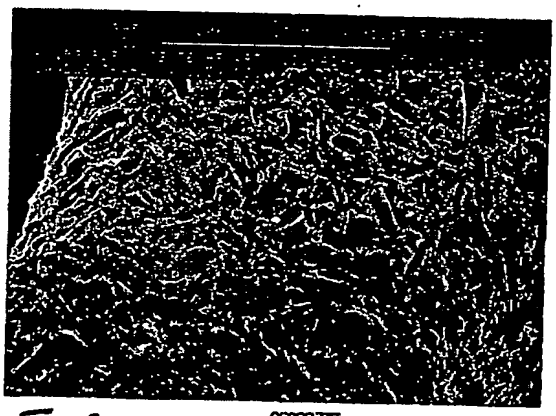


Fig 6 05022.TIF 688×560×256 gr

Fig 7 05023.TIF 712×572×256 gr

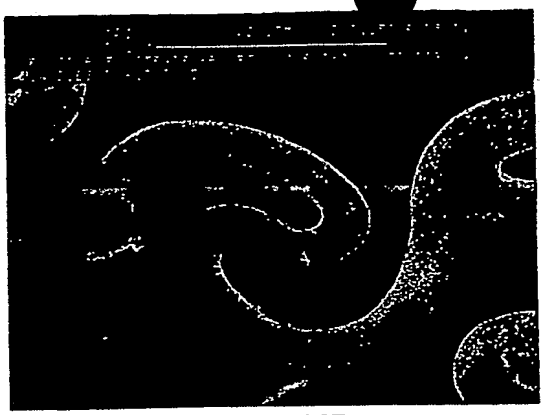


Fig 8 05024.TIF 688×660×256 gif

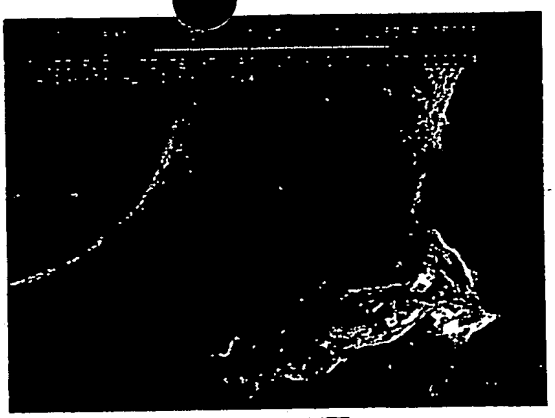


Fig 9 05025.TIF 688×660×256 gif

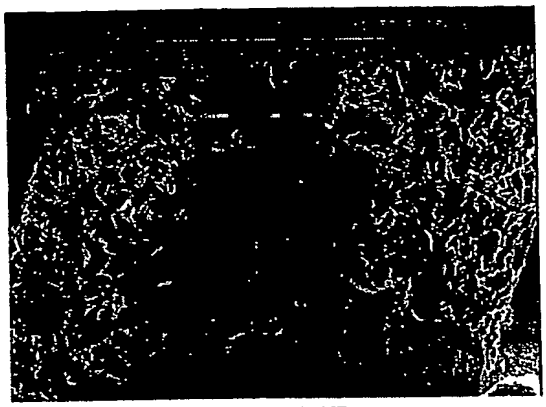


Fig 10 05026.TIF 688×660×256 gif

Fig 11 05027.TIF 712×572×256 gif

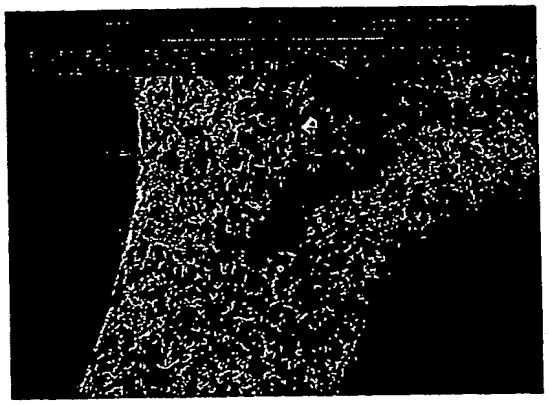


Fig 12 05028.TIF 688×660×256 gif

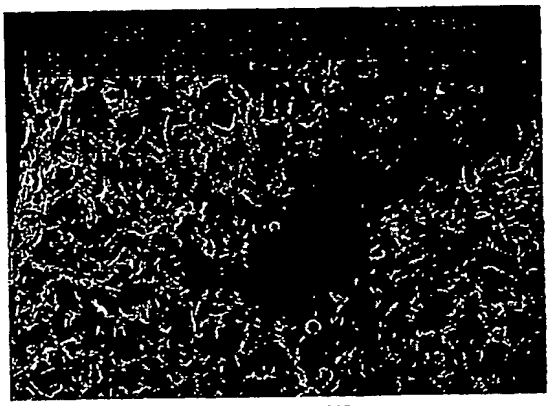


Fig 13 05029.TIF 688×660×256 gif

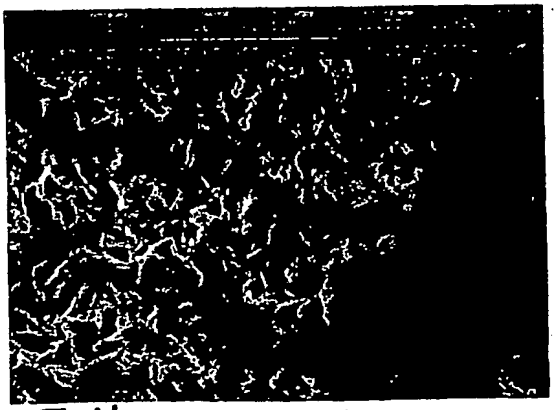


Fig 14 05030.TIF 712×572×256 gif

Figure 15

Lot # 094846
Article # 310S1635
Target dose 230 µg

Table 1

	shipped	sample #
drug-content-RCC (3)	14.08.02	5971-5979
drug-release-RCC (3)	14.08.02	5980-5982
DMAC-RCC (1)	0	
samples for ageing		result:
samples for additional tests		

= Felder für Einträge

Content - results
Date of content: 16.08.02

Table 2

Sample #	Target Dose [µg/Stent]	Content [µg/Stent]	Content mean [µg/Stent]	STDEV [µg]	CV [%]	Target Deviation [%]
5971		223				
5978	230	189	205	17,0	8,30	-10,7
5979		204				

Figure 16

Table 3

Release only [µg]	% Release of content	Stent only* [µg]	% of content	Release+ Stent [µg]	% of content
99,0	48,2		0,0	99,0	48,2
107,0	52,1		0,0	107,0	52,1
111,0	54,1		0,0	111,0	54,1
105,7	51,5	0,0	0,0	105,7	51,5

*) extraction after release test

Release
CT Lots with new method (pH6)

Single values [µg Tacrolimus]

Table 4

Wavelength: 210 nm

sample #	time [hours] 0,16	0,5	1	4	6	24	48	72	96
5980	17	19	12	14	6	15	12	3	1
5981	22	18	10	14	7	15	13	6	2
5982	27	18	9	14	6	15	13	7	2
Average	22,0	18,3	10,3	14,0	6,3	15,0	12,7	5,3	1,7

Figure 17

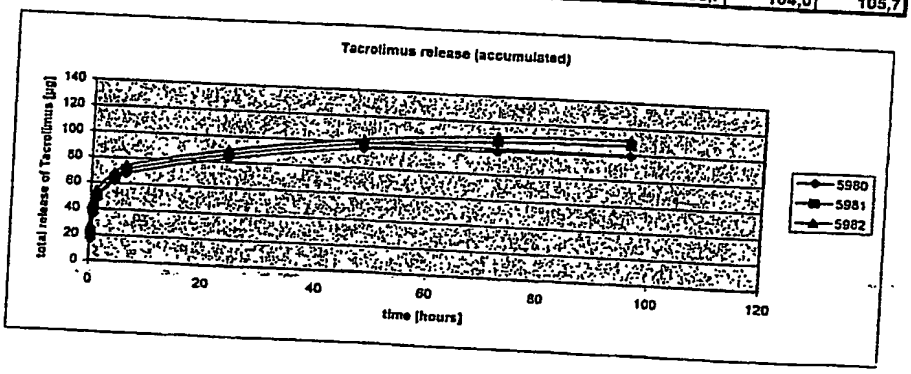
Accumulated values [µg Tacrolimus]

Table 5

1 = < 2 µg

sample #	time [hours] 0,16	0,5	1	4	6	24	48	72	96
5980	17	36	48	62	68	83	95	98	99
5981	22	40	50	64	71	86	99	105	107
5982	27	45	54	68	74	89	102	109	111
Average	22,0	40,3	50,7	64,7	71,0	86,0	98,7	104,0	105,7

Figure 18



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